

Granulomatous Inflammation

Objectives:

- Define Granulomatous inflammation.
- Recognize the morphology of granulomas (tubercles) and list the cells found in granuloma along with their appearance.
- Understands the pathogenesis of granuloma formation.
- Identify the two types of granulomas, which differ in their pathogenesis.
 - Foreign body granuloma
 - Immune granulomas
- List the common causes of Granulomatous Inflammation.

Color Index:

Slides

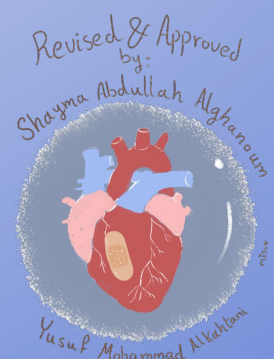
Important

Male's slides only

Female's slides only

Notes

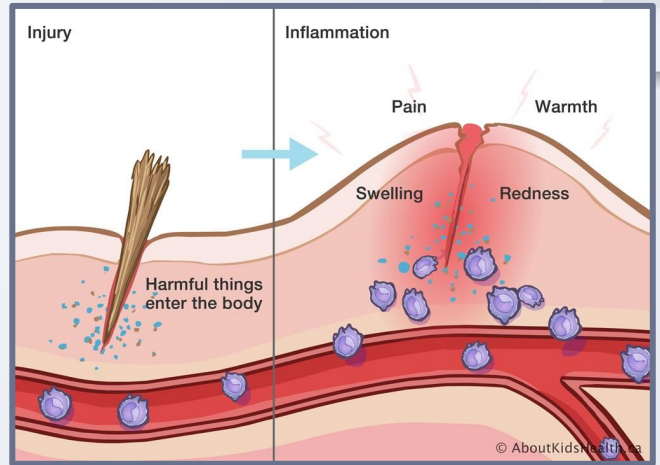
Extra information



Inflammation

Remember: (Inflammation Lecture)

Inflammation: is a local response to tissue injury. Any tissue that reacts to cellular injury or injurious agent will cause inflammation. It is a defense mechanism against any agent that comes from outside the body.



Types of inflammation :

Acute inflammation

Neutrophils

Chronic inflammation

Macrophages

lymphocytes

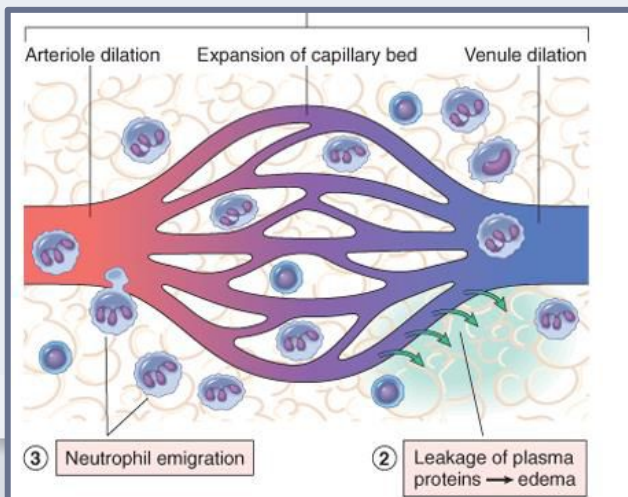
plasma cells

1) Acute inflammation

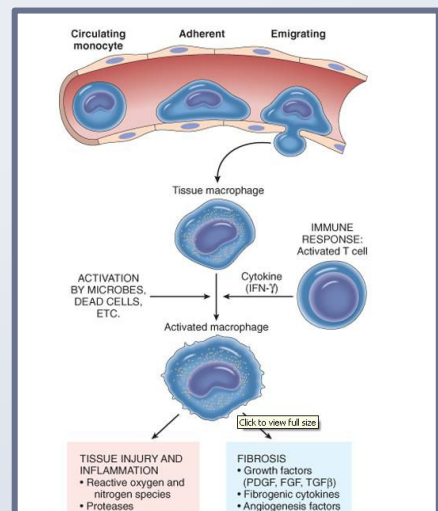
Neutrophils immediately respond to acute inflammation

2) Chronic inflammation

Macrophages, lymphocytes, and plasma cells take place in chronic inflammation



Acute inflammation



Chronic inflammation

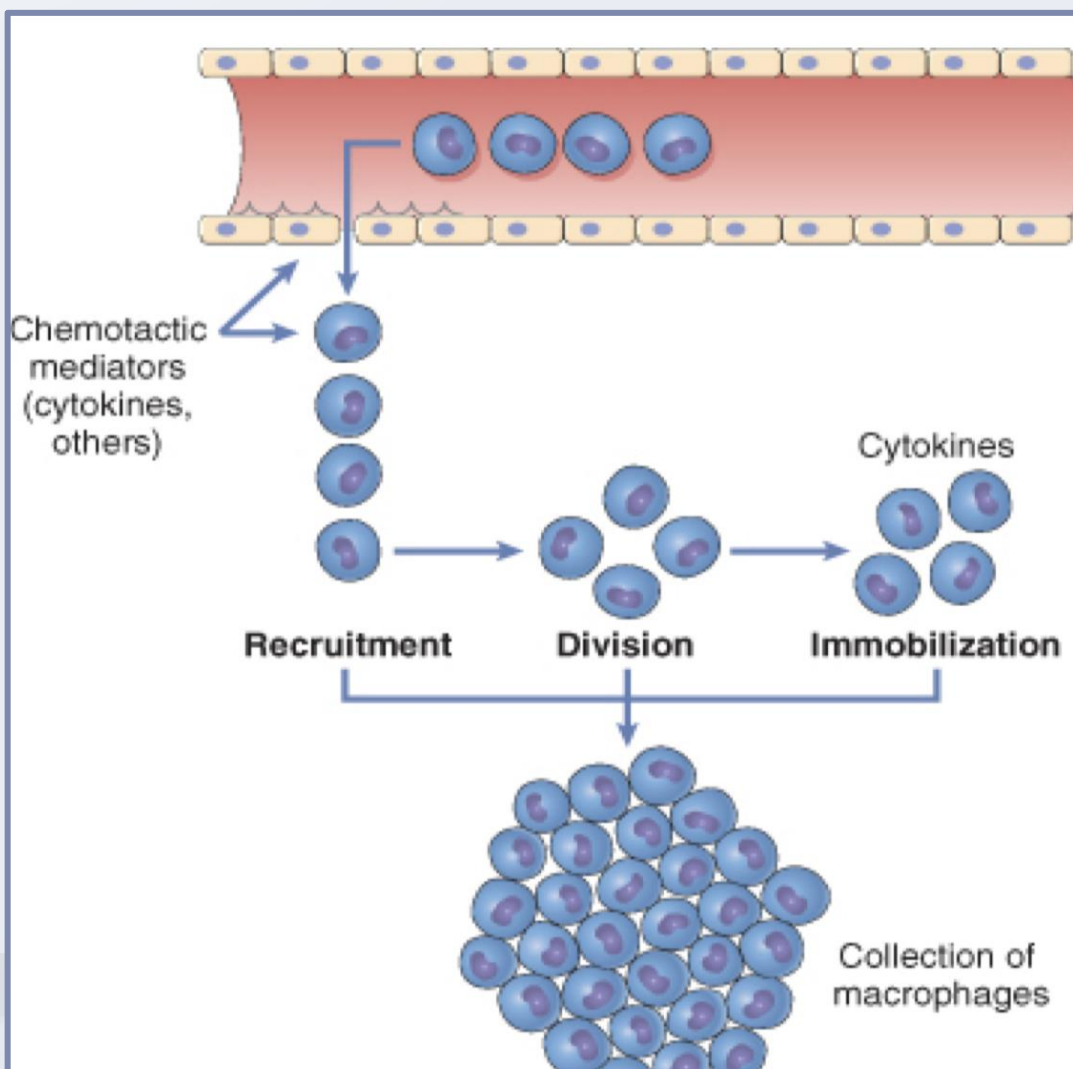
Inflammation cont.

From Female's slides

The **activated macrophages** may develop abundant cytoplasm and begin to resemble epithelial cells, and are called **epithelioid cells**.

Epithelioid histiocytic cells are the **principle cellular components in granuloma**

Granuloma is a collection of:
epithelioid cell (activated macrophage).



Granulomatous inflammation

****This whole slide is from team (extra) to clarify some concepts.**

Granulomatous inflammation is a type of chronic inflammation that is characterized by the presence of granulomas.

When the immune system is unable to eliminate foreign substances, it forms granulomas to try to **"wall off"** these foreign substances.

Our bodies form granulomas to:

A- **Contain and try to prevent the spreading** of the area of *bacterial, parasitic, or fungal infection*.

(this is what happens in immune granuloma = cell mediated immune response)

OR

B- **Isolate foreign objects or irritants**.

(this is what happens in foreign body granuloma = no specific inflammatory immune response)

A granuloma is:

Localized: restricted to a specific place &

Nodular: made up of clumps of immune cells

Main structural components of granulomas:

- **Epithelioid cells:** activated macrophages/histiocytes (are the main component, resemble epithelial cells)
- **Multinucleated giant cells:** fusion of adjacent epithelioid cells (Langhans or foreign body)
- **Lymphoid cells**
- **Necrosis** (only in some granulomas e.g. central caseous necrosis of tuberculosis)

1. Engulfment by Macrophage

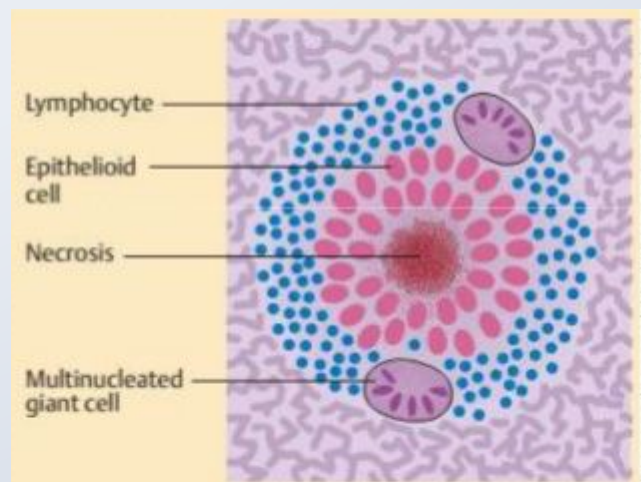
- Unable to eat foreign substance
- Undergo morphologic changes to become epithelioid cells (**activation**)

2. CD4+ T cells

- When macrophage fails to kill organism
- It presents it to CD4+ cells

3. Cytokines

- IL-1 and IL-2, interferon- γ , TNF- α
- Fibroblast proliferation



Granulomatous inflammation

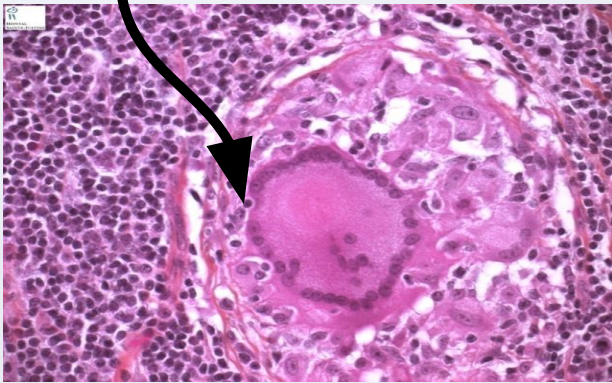
Granulomatous inflammation:

A form of chronic inflammation characterized by the formation of granulomas.

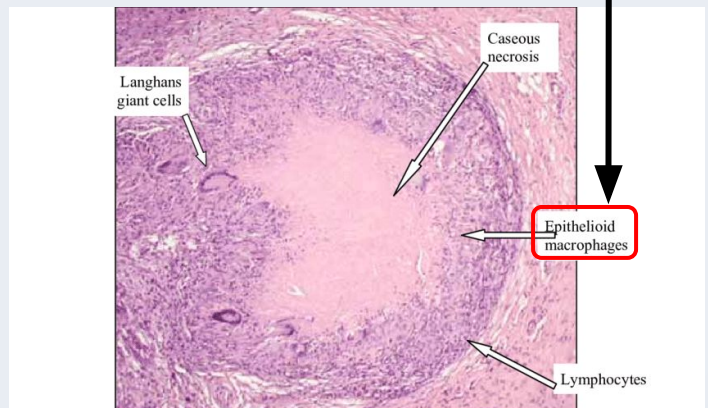
Granuloma:

- Nodular collection of epithelioid macrophages surrounded by a rim of lymphocytes.
- Collections of activated macrophages, often with T-lymphocytes, and sometimes associated with central necrosis.

Some activated macrophages may fuse, forming multinucleated **giant cells**.

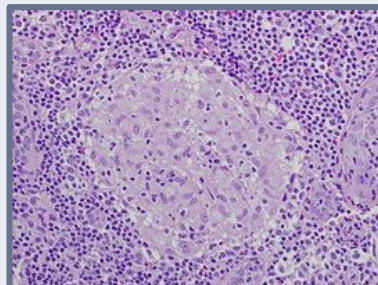


Epithelioid macrophages:
squamous cell like appearance



Why are granulomas important?

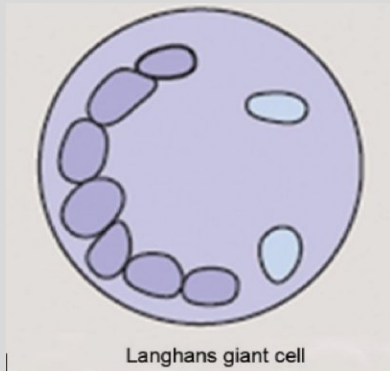
- Granulomas are encountered in certain specific pathologic states.
- Recognition of the granulomatous pattern is important because of the limited number of conditions (some life threatening) that cause it.



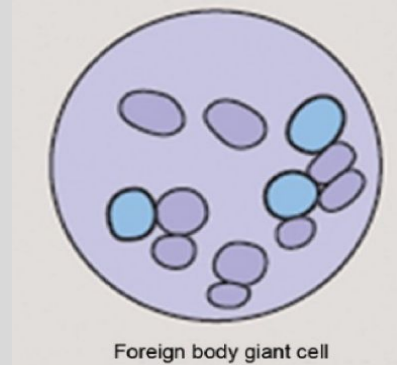
Granuloma

Arrangement of nuclei in giant cells

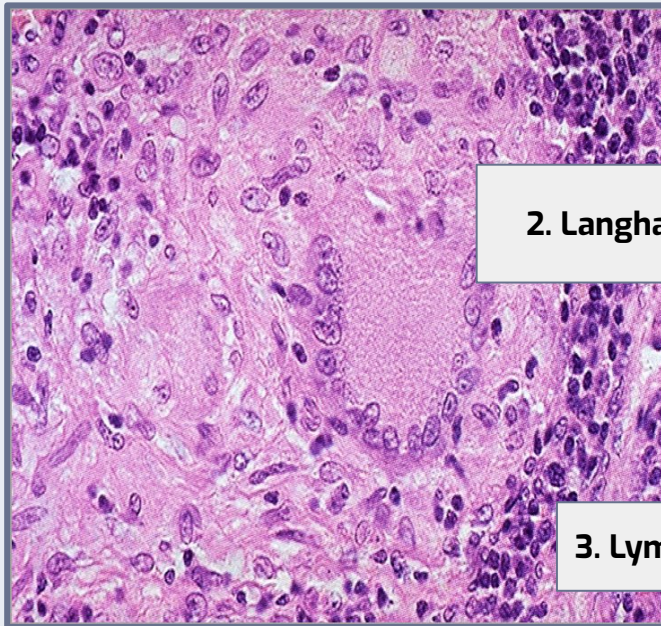
Peripheral (Seen in TB)
(Langhans- type giant cell)



haphazard (anywhere)
(foreign body-type giant cell)



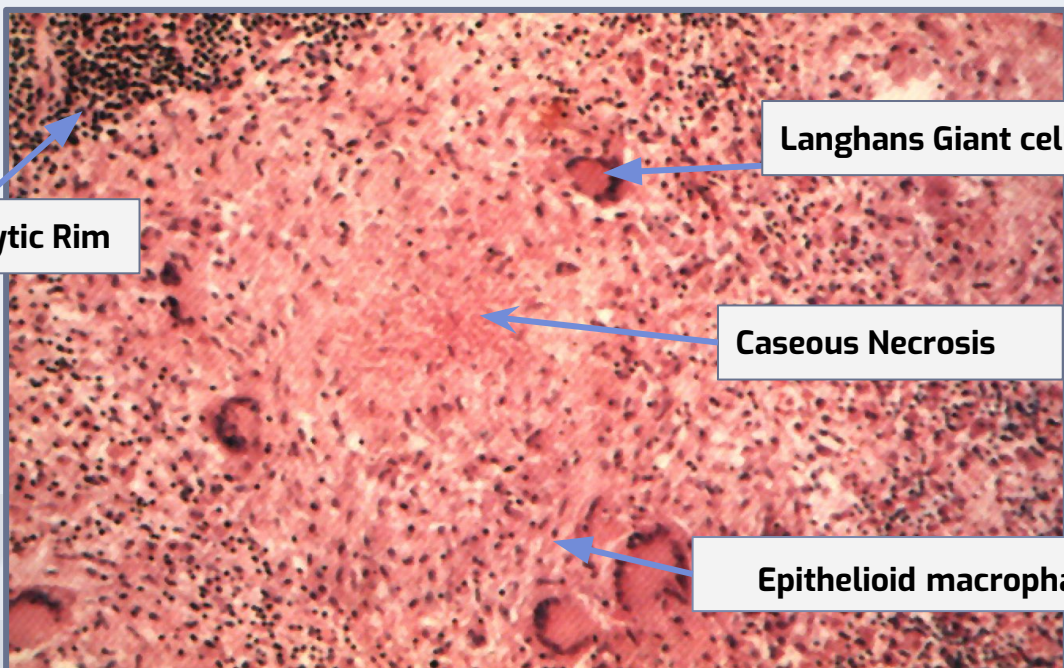
1. microscopic aggregation of activated macrophages

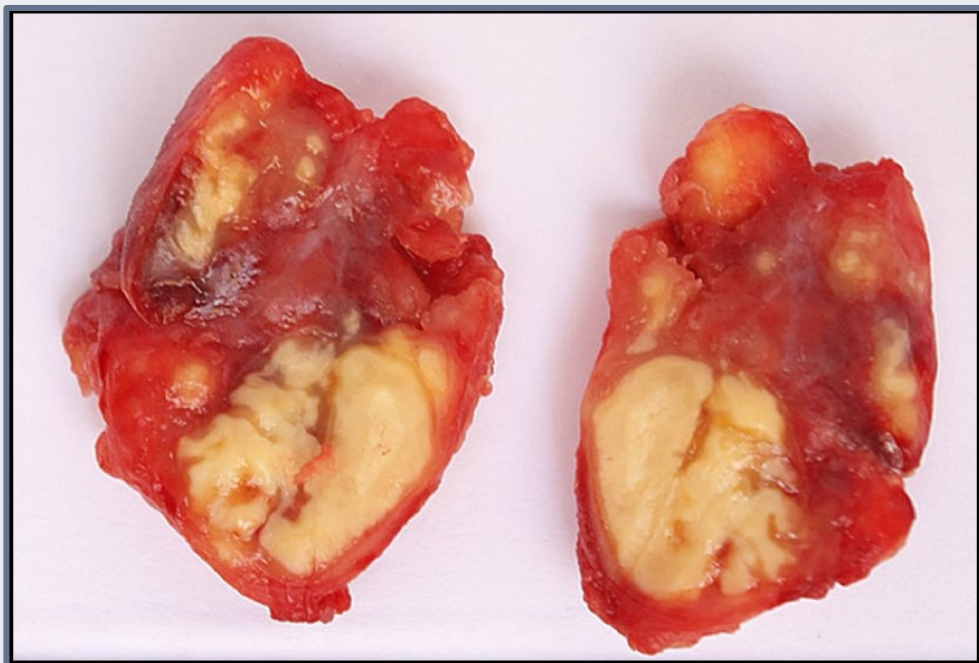
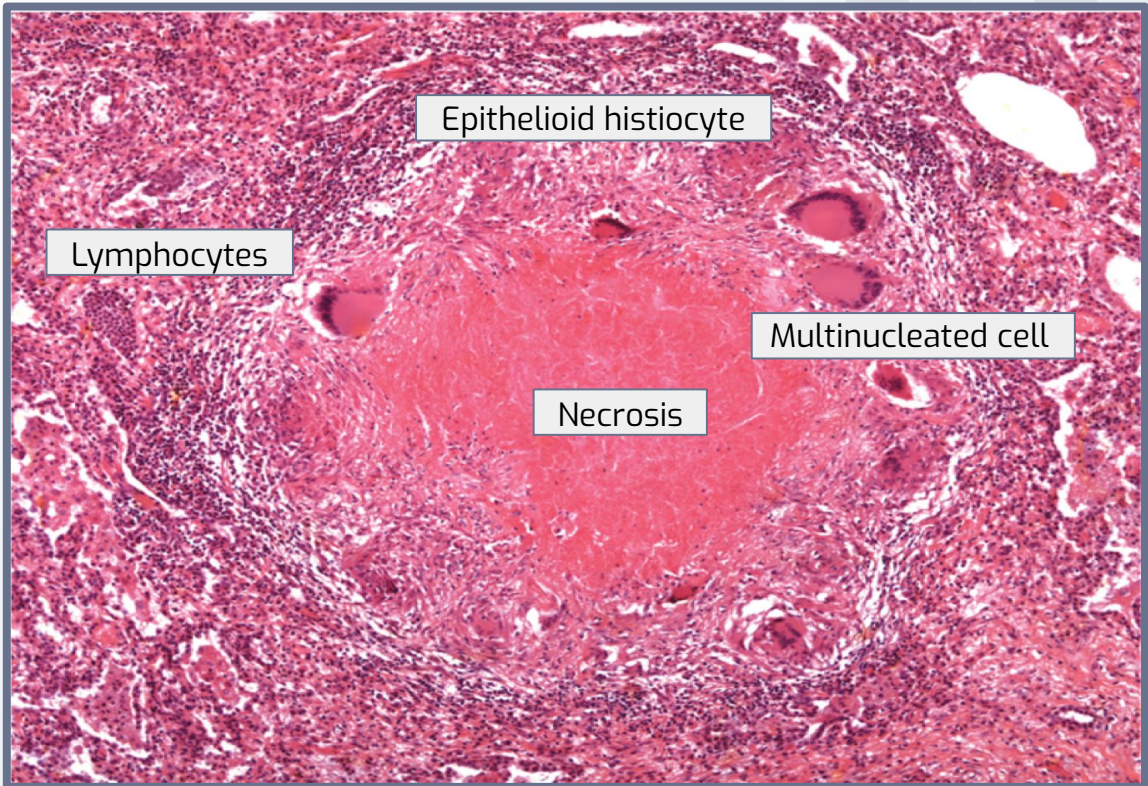


2. Langhans-type giant cell

3. Lymphocytes

Lymphocytic Rim





Section of a lymph node with caseation necrosis

Most common cause of caseous necrosis is? TB (not the only cause)

Granulomatous Inflammation pathogenesis :

- Neutrophils ordinarily remove agents that incite an acute inflammatory response.
- *However*, There are circumstances in which reactive neutrophils cannot digest the substances that provoke chronic inflammation.

Granulomatous Inflammation mechanism

What is the initiating event in granuloma formation?

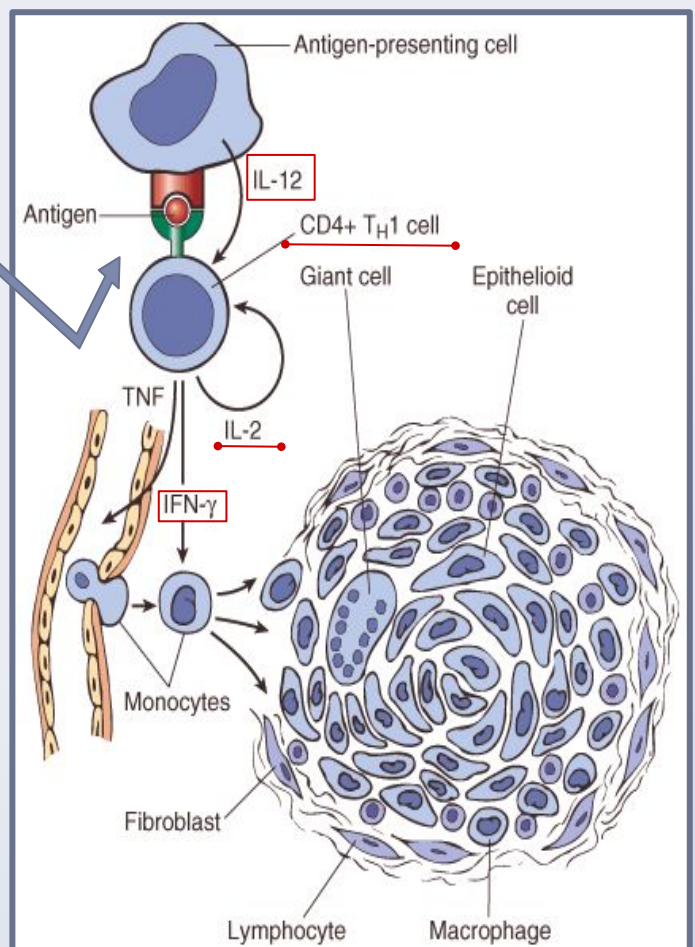
Deposition of *indigestible* antigenic material.

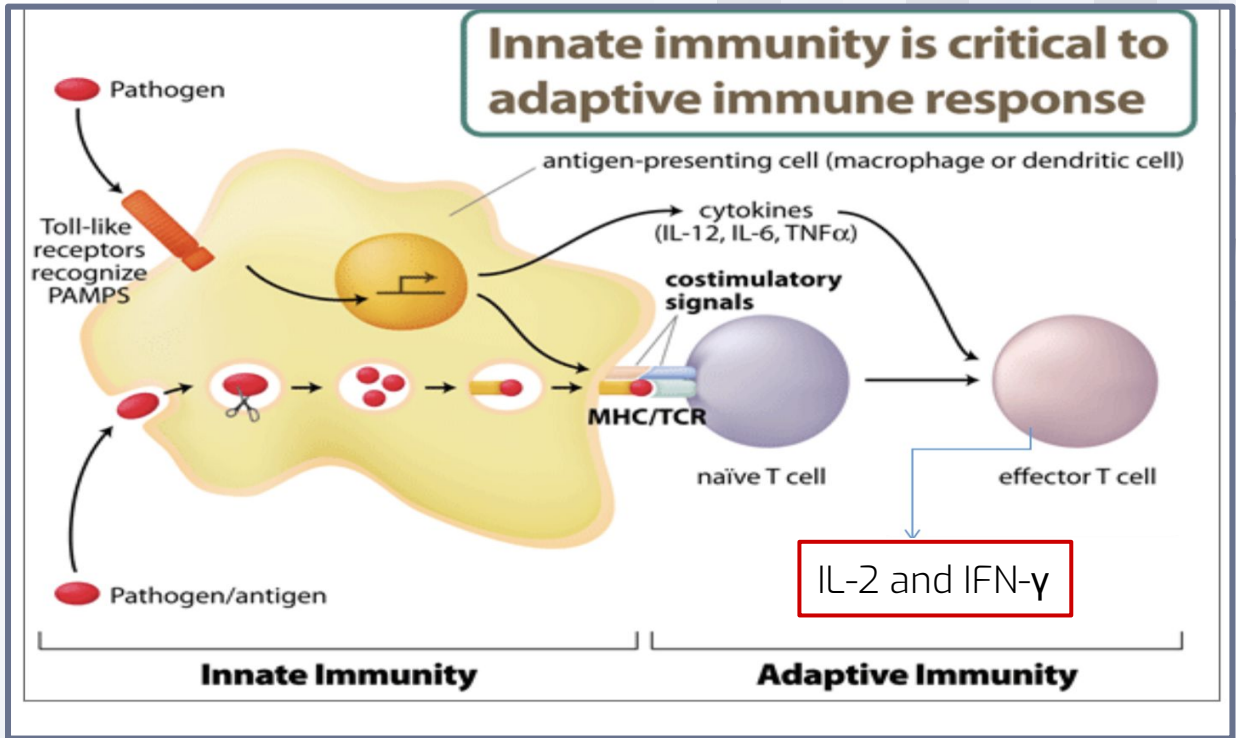
→ **IFN- γ** released by the **CD4+ T cells** of the TH1 subset.

→ **IFN- γ** helps to activate and convert macrophages into epithelioid cells in the process of granuloma formation

indigestible antigenic material

Type IV hypersensitivity
(Cell mediated immunity)





Male's slides

Epithelioid Cell granulomas

1st

When macrophages have successfully phagocytosed the injurious agent but it survives inside them.

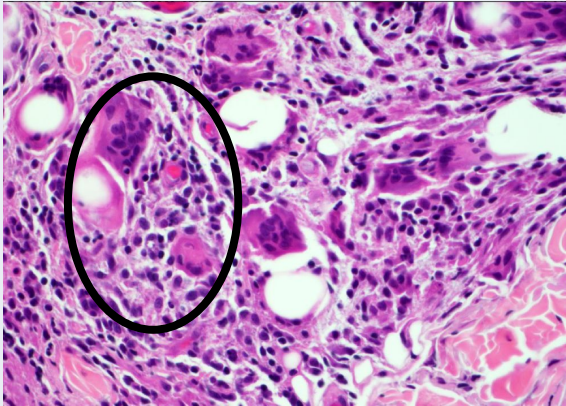
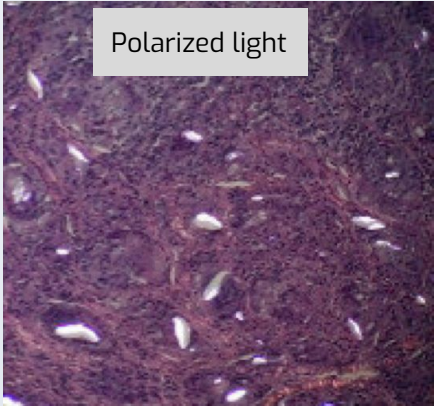
2nd

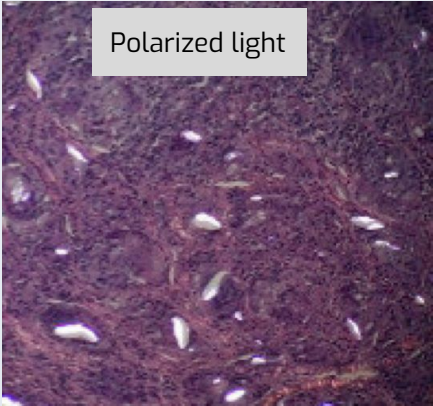
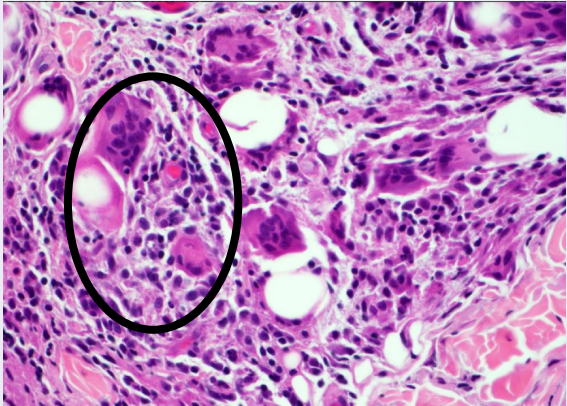
Then, an active T-lymphocyte mediated cellular immune response occurs. Lymphokines produced by activated T-lymphocytes inhibit migration of macrophages and cause them to aggregate in the area of injury and form granulomas.

Examples of Diseases with Granulomatous Inflammation

| Disease | Cause | Tissue Reaction |
|---------------------|--|--|
| Tuberculosis | <i>Mycobacterium tuberculosis</i> | Caseating granuloma (tubercle): focus of activated macrophages (epithelioid cells), rimmed by fibroblasts, lymphocytes, histiocytes, occasional Langhans giant cells; central necrosis with amorphous granular debris; acid-fast bacilli |
| Leprosy | <i>Mycobacterium leprae</i> | Acid-fast bacilli in macrophages; noncaseating granulomas |
| Syphilis | <i>Treponema pallidum</i> | Gumma: microscopic to grossly visible lesion, enclosing wall of histiocytes; plasma cell infiltrate; central cells are necrotic without loss of cellular outline |
| Cat-scratch disease | Gram-negative bacillus | Rounded or stellate granuloma containing central granular debris and neutrophils; giant cells uncommon |
| Sarcoidosis | Unknown etiology | Noncaseating granulomas with abundant activated macrophages |
| Crohn disease | Immune reaction against intestinal bacteria, self antigens | Occasional noncaseating granulomas in the wall of the intestine, with dense chronic inflammatory infiltrate |

Types of granulomas (differ in their pathogenesis)

| | 1. Foreign Body Granuloma | 2. Immune Granuloma |
|----------------|--|--|
| (Pathogenesis) | Cause relatively inert (خامل) foreign bodies that do not incite any specific inflammatory immune response | a variety of agents that are capable of inducing a T cell mediated immune response |
| | <i>Typically agents are:</i> large enough to preclude phagocytosis by a single macrophage, do not incite any specific inflammatory immune response | <i>Typically agents are:</i> persistent and insoluble Particles (microbes) that are capable of inducing a cell-mediated immune response . |
| | Examples: <ul style="list-style-type: none"> • <u>Talc</u> (associated with intravenous drug abuse) • <u>Sutures</u> • <u>Graft material</u> | Examples: <u>Bacteria:</u> <ul style="list-style-type: none"> • Tuberculosis • Leprosy • Actinomycosis • Cat-scratch disease <u>Parasites:</u> <ul style="list-style-type: none"> • Schistosomiasis • Leishmaniasis <u>Fungi:</u> <ul style="list-style-type: none"> • Histoplasmosis • Blastomycosis <u>Metal/Dust:</u> <ul style="list-style-type: none"> • Berylliosis |
| | Identification of foreign body: <ul style="list-style-type: none"> - Is done using <u>polarized light</u> (foreign body appears refractile) - Foreign body is <u>in center of granuloma</u> | |
| |  |  |



Polarized light

3. Diseases in which the cause of the granuloma is *unknown*:

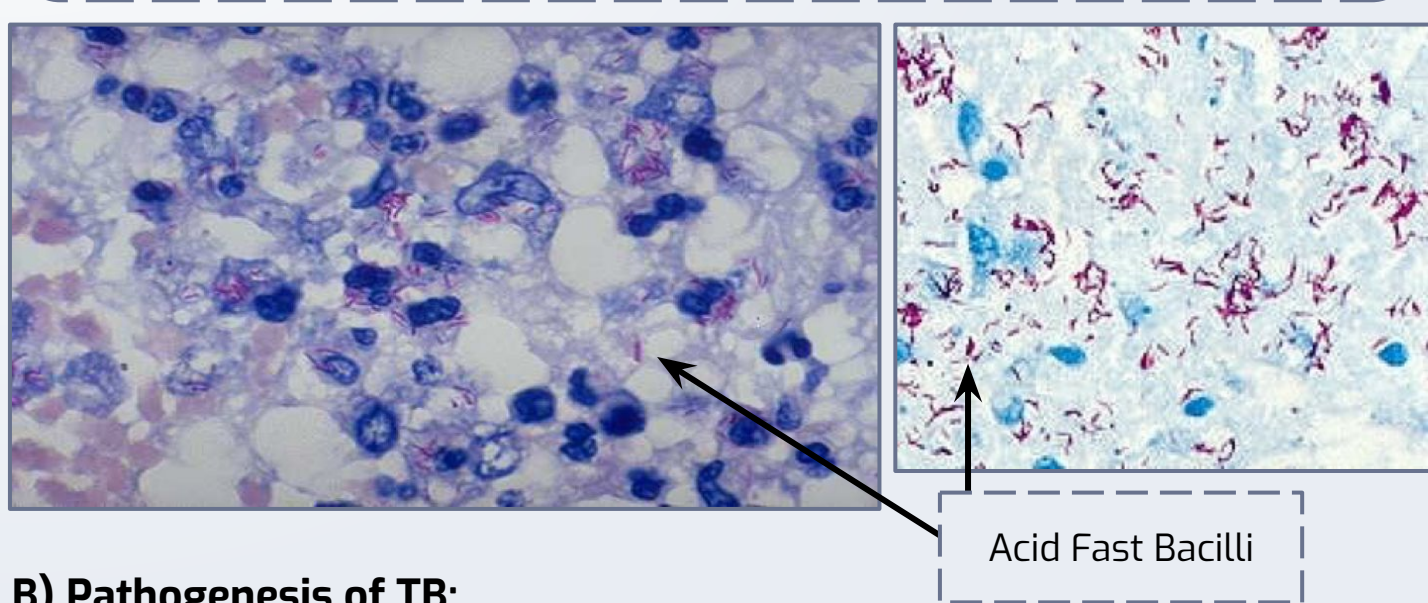
- Sarcoidosis
- Crohn's disease (idiopathic inflammatory bowel disease)

Types of granulomas (Immune Granulomas)

1. Tuberculosis: Mycobacterium tuberculosis

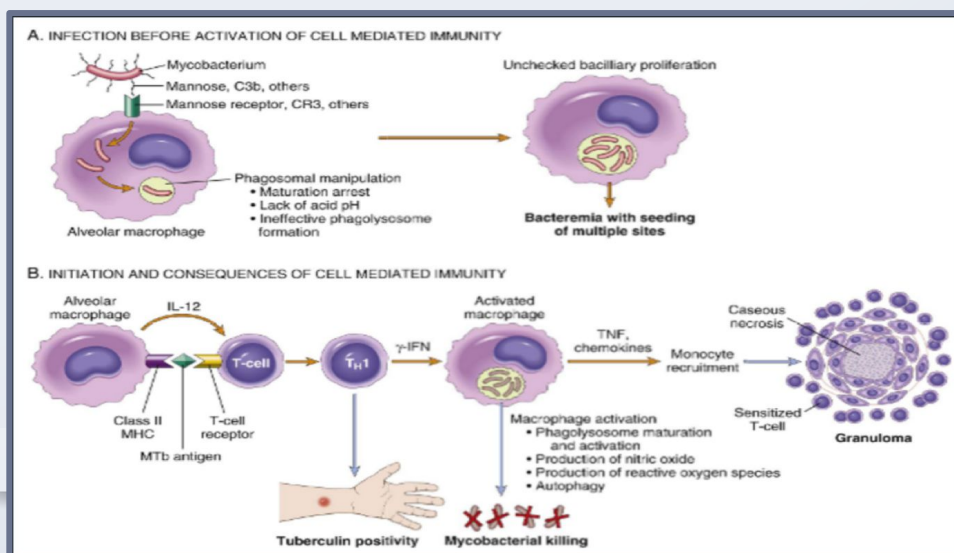
A) TB is a Mycobacteria:

- **Big Bacilli** (Fungus like)
- Slender rods
- **Acid fast bacilli (AFB)** have a high content of complex lipids that readily bind the Ziehl-Neelsen (carbol fuchsin) stain and subsequently resist decolorization)



B) Pathogenesis of TB:

- **Cord factor** is a glycolipid molecule found in the cell wall of Mycobacterium tuberculosis and similar species E.g. TB bacilli.
- Cord factor presence increases the production of the **cytokines interleukin 12** (IL 12, IL 1, β , IL 6 and TNF which are all pro inflammatory cytokines important for granuloma formation.
- It **prevents phagosomal function** (by maturation arrest).

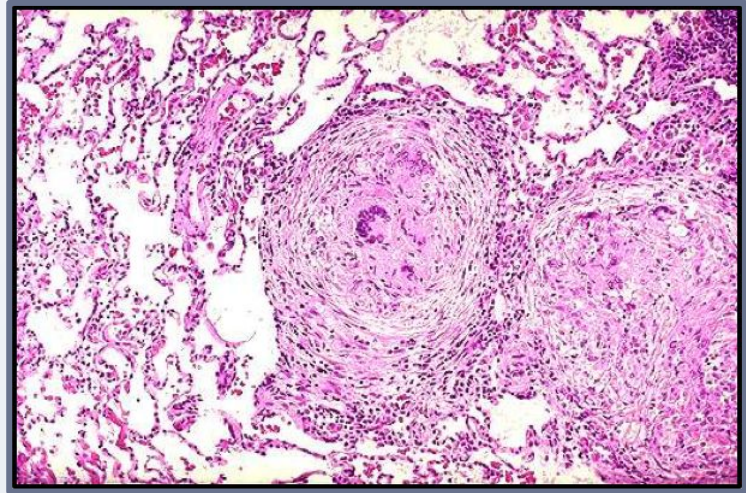


Types of granulomas (Immune Granulomas)

1. Tuberculosis: *Mycobacterium tuberculosis*

What is the most common cause of caseous necrosis?

Tuberculosis



Male's slides

C) Signs, Symptoms, and Diagnosis of TB

Diagnosis Methods:

- Tuberculin skin testing (TST).
- PCR: identification & drug resistance.
- Acid fast stain (>10,000 CFU/ml).
- Bronchoscopy.

-X-ray



Any long-standing cough with or without fever could be Tuberculosis (TB)!

Do you have...



...a cough longer than 14 days?



...fever of long duration?



...shortness of breath?



...blood in your cough?



...tiredness?



...chest pain?



...loss of appetite?



...weight loss?



...night sweats?

It could be TB.

-Sputum smear microscopy



-Culture

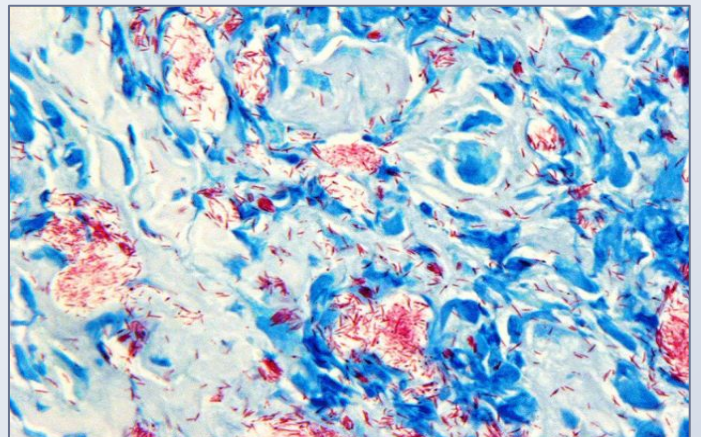
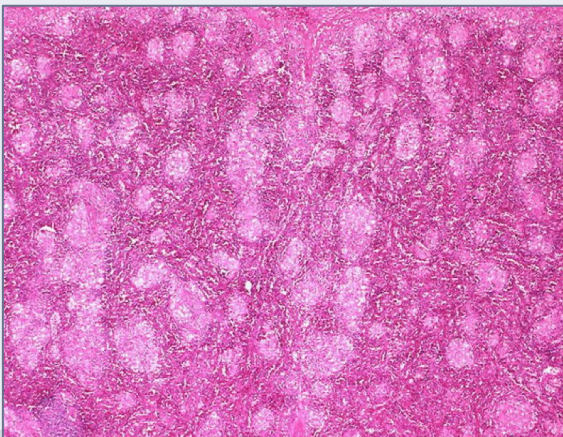
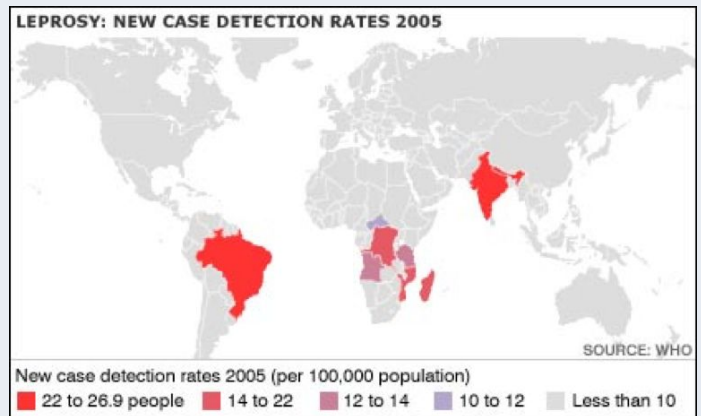
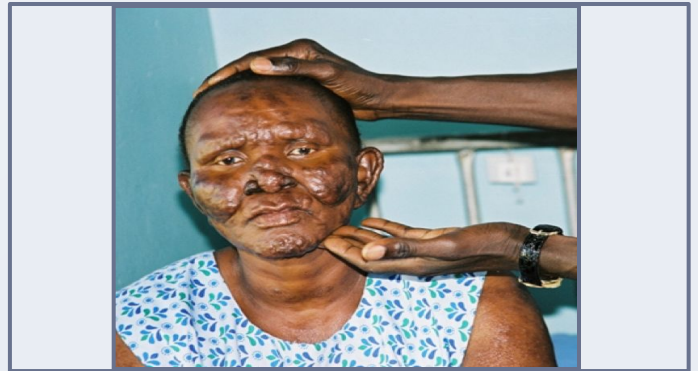


Types of granulomas (Immune Granulomas)

2. Leprosy

Leprosy:

- Bacterial infection (*Mycobacterium leprae*)
- Acid Fast Bacilli (like TB, remember?)
- Many granuloma in skin, around nerve (overtime causes loss of sensation → autoamputation)

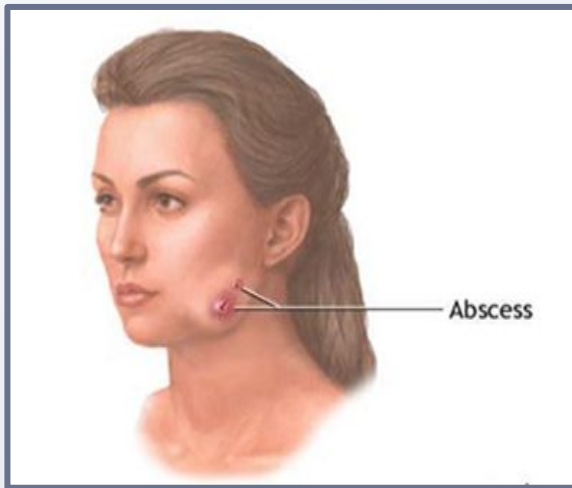


Types of granulomas (Immune Granulomas)

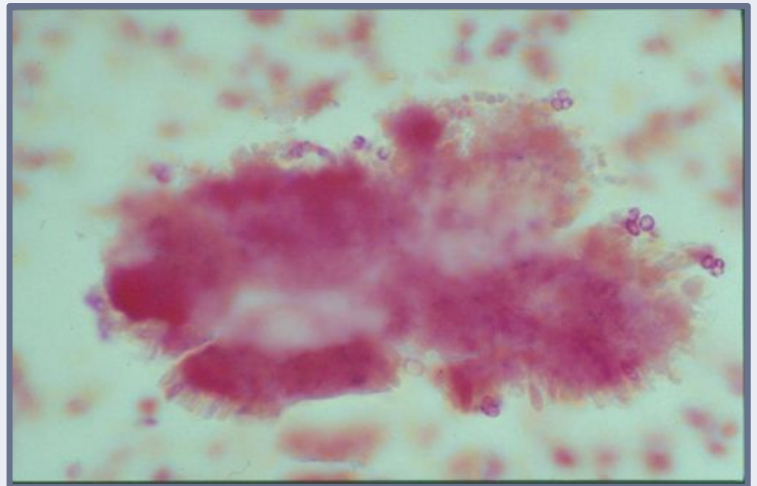
3. Actinomyces

Actinomyces:

- Bacterial infection
- Long-term (chronic) granulomatous bacterial infection that commonly affects the face and neck
- Examination of drained fluid under a microscope shows **"sulfur granules"** in the fluid. They are yellowish granules made of clumped organisms.



Bacteria are normally found in the saliva, cause damage only when they go deep in tissue

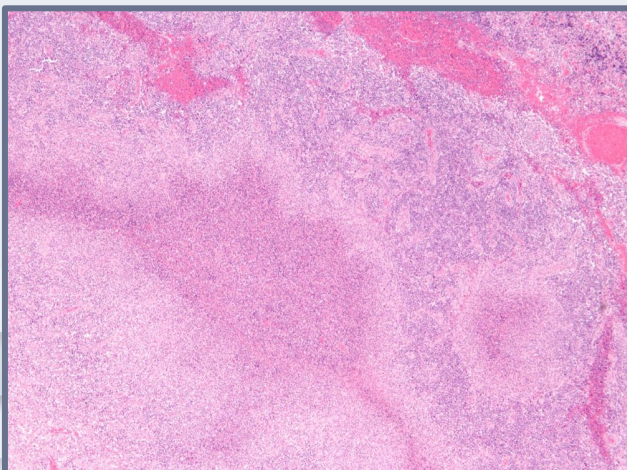


Filamentous, gram-positive, no-acid-fast, anaerobic-to-microaerophilic bacteria

4. Cat-scratch Disease

Cat-scratch Disease:

- Bacterial infection; Gram-negative bacillus
- Rounded or stellate granuloma containing central granular debris and neutrophils.

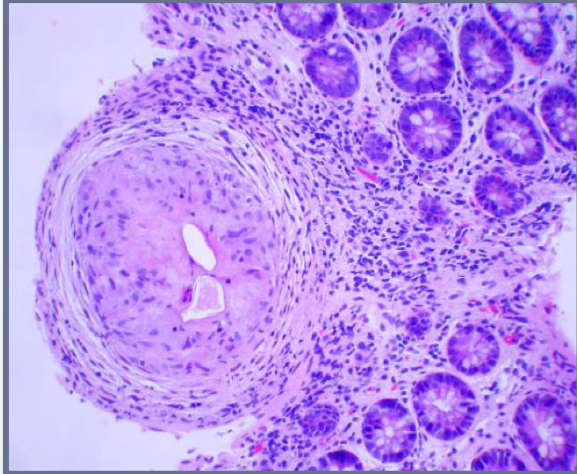


Types of granulomas (Immune Granulomas)

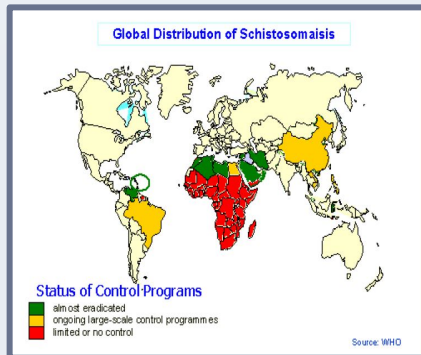
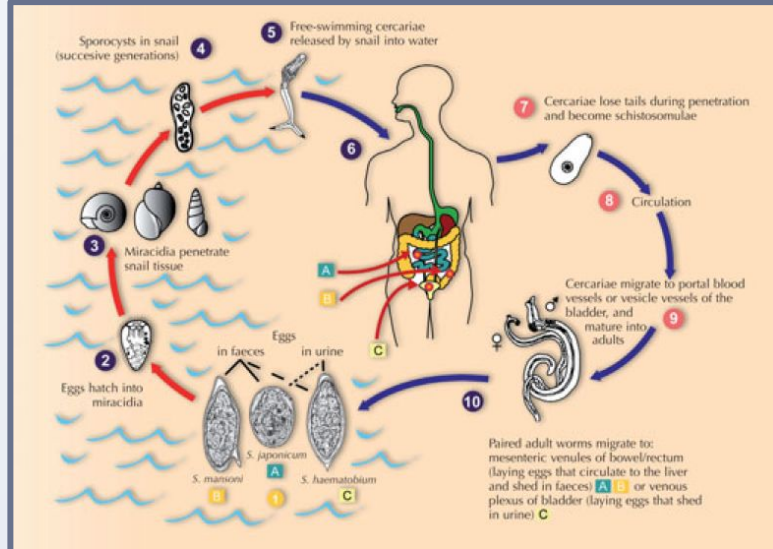
5. Schistosomiasis

Schistosoma:

- **Parasitic infection**
- **Granuloma** is associated with **eosinophils**



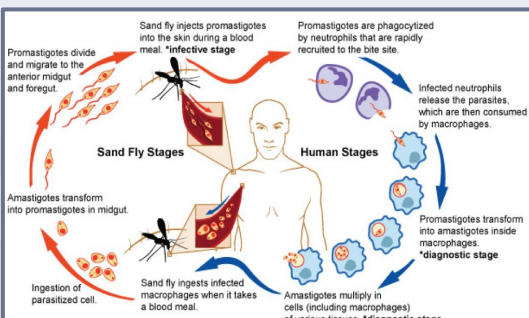
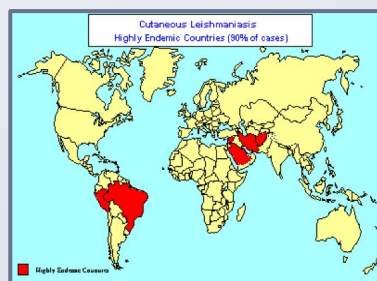
In parasitic infections, the granuloma is associated with eosinophils.



6. Leishmaniasis

Leishmaniasis:

- **Parasitic infection**
- **Excess histiocytes** in affected area
- Caused by **sandfly** bite

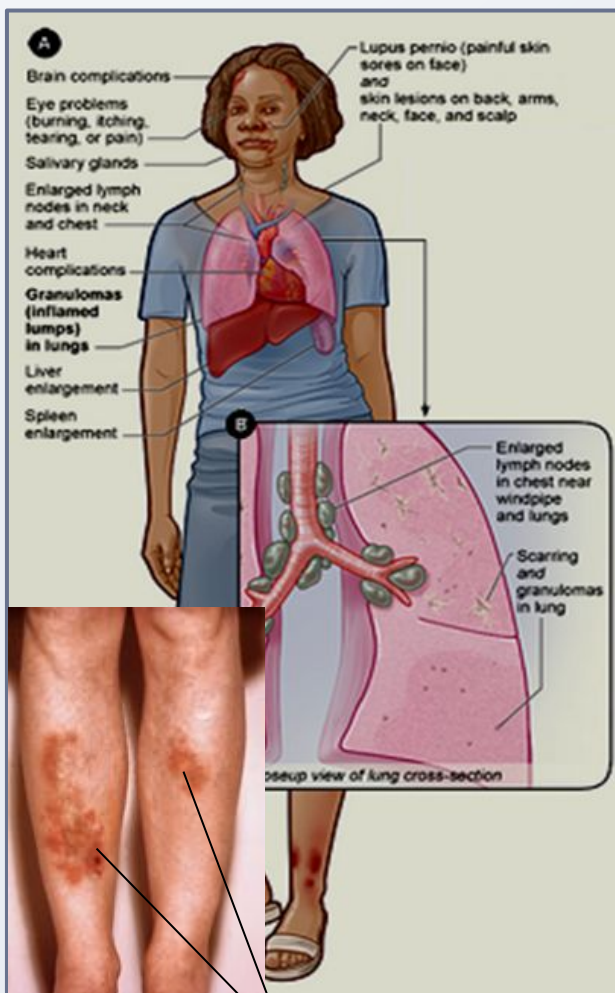


Types of granulomas (unknown cause)

7. Sarcoidosis

Sarcoidosis:

- Unknown cause of granuloma
- Affects multiple organs
- **Non-caseating granuloma**
- Enlargement of bilateral hilar lymph nodes



Non-caseating granuloma



Enlargement of bilateral hilar lymph nodes

Summary:

- **Epithelioid histiocytes:** the most important cell in granulomatous inflammation.
- **IFN- γ :** a cytokines that is important in activating macrophages and transforming them into epithelioid cells.
- **Langhans cells:** multinucleated cell in TB (Langhans' giant cells)
- **Langerhans cells:** antigen presenting dendritic cells (in skin).
- **Type IV hypersensitivity reaction:** pathogenesis of immune type granulomatous inflammation .
- **Caseating Granuloma:** microscopic finding of TB.
- **Cord Factor:** found in the cell wall of TB.
- **Granulation tissue:** (tissue of repair) contains new small blood vessels, fibroblasts, and mononuclear cells in an edematous extracellular matrix; it is part of the repair response.
- **Granuloma:** (cell mediated immunity, consists of activated histiocytes) is circumscribed collection of epithelioid cells, usually surrounded by lymphocytes; it is a form of chronic inflammation.

Causes of granulomatous inflammation

1. Bacterial (e.g. Mycobacterium tuberculosis, M. leprae, Treponema pallidum)

2. Parasitic (e.g. schistosomiasis)

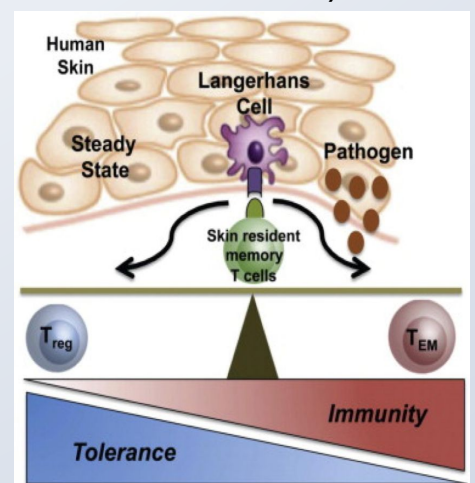
3. Fungal (e.g. Histoplasmosis, blastomycosis)

4. Inorganic dusts (e.g. Silicosis, berylliosis)

5. Foreign body

6. Unknown (e.g. sarcoidosis)

Langerhans cells are antigen presenting cells (in the skin)



Quiz:

1. Which of the following diseases does not cause granulomatous inflammation ?

- A. Cat-scratch disease
- B. Actinomycosis
- C. Sarcoidosis
- D. Leishmaniasis
- E. Staphylococcus infection

Answer: E. Staphylococcus infection (*Pyogenic infection: Pus forming*)

2. What are the causes of Caseous Necrosis?

Answer: Caseous necrosis is caused by Tuberculosis, leprosy, and fungal infections.

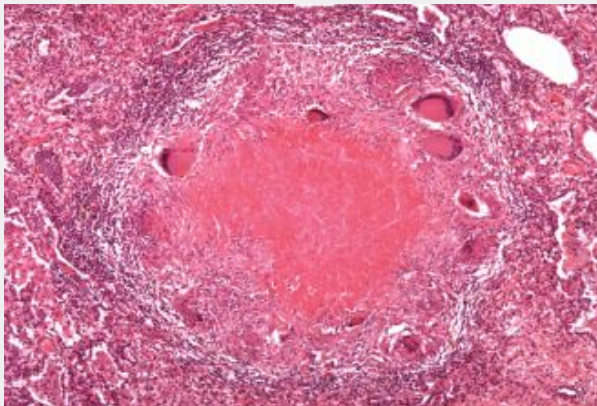
- Leprosy granulomas are in **skin** while Tuberculosis and fungal infections are in **lung**.
- So, leprosy is easy to differentiate clinically (from the other two).
- To differentiate between tuberculosis and fungal infections (both in lung), we must stain both (Ziehl-Neelsen stain for TB).

3. How does caseous necrosis differ from coagulative necrosis under the microscope?

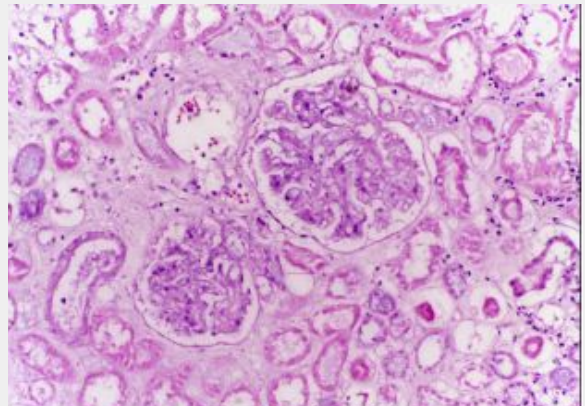
Answer:

In caseous necrosis, there is **total loss** of tissue structure

In coagulative necrosis, cell outlines are retained



Caseous necrosis



Coagulative necrosis

Quiz:

4. What is the origin of epithelioid cells?

Answer: They are transformed/modified macrophages

5. What is the difference between granulation tissue and granulomatous inflammation?

Answer:

Granulation tissue (*tissue of repair*) contains new small blood vessels, fibroblasts, and mononuclear cells in an edematous extracellular matrix; it is part of the repair response.

A granuloma is a circumscribed collection of epithelioid cells, usually surrounded by lymphocytes; it is a form of chronic inflammation (*it is a cell mediated immunity consisting of activated epithelioid histiocytes*)

6. What are the causes of granulomatous inflammation?

Answer: Causes are

- 1) Bacterial (e.g. mycobacterium tuberculosis. M. Leprae, Treponema, Pallidum)
- 2) Parasitic (e.g. schistosomiasis)
- 3) Fungal (e.g. histoplasmosis, blastomycosis)
- 4) Inorganic dusts (e.g. silicosis, berylliosis)
- 5) Foreign body
- 6) Unknown (e.g. sarcoidosis)

7. How are giant cells formed in granulomas?

Answer: Giant cells are formed by fusion of macrophages

8. What are the other cells in granuloma?

Answer: Lymphocytes (mainly CD4+), that caused the granulomatous reaction are present. Healing granulomas are surrounded by fibroblasts.

9. In TB, do granulomas in different organs look different?

Answer: No, all granulomas look similar histologically/morphologically (all are caseating granuloma)

TAKE HOME MESSAGES:

- ★ Granulomatous inflammation is a distinctive pattern of chronic inflammation characterized by aggregates epithelioid macrophages.
- ★ Damaging stimuli which provoke a granulomatous inflammatory response include: Microorganisms which are of low inherent pathogenicity but which excite an immune response.
- ★ Granuloma are produced in response to:
 - 1-Bacterial infection
 - 2-parasitic infection: e.g. Schistosoma infection
 - 3-Certain fungi cannot be dealt with adequately by neutrophils, and thus excite granulomatous reactions.
 - 4-Non-living foreign material deposited in tissues, e.g. keratin from ruptured epidermal cyst.
 - 5-Unknown factors, e.g. in the disease 'sarcoidosis' and Crohn's disease

1- Which of the following is a Diagnosis Method for Tuberculosis (TB) ?

| | | | |
|--------|--------|--------------------|----------------|
| a- TST | B- PCR | C- Acid fast stain | D- All of them |
|--------|--------|--------------------|----------------|

2- Which of the following is a pathogen for Immune Granuloma ?

| | | | |
|-------------|------------|---------------|----------------|
| A- Bacteria | B- Viruses | C- Antibiotic | D- All of them |
|-------------|------------|---------------|----------------|

3-Which of the following doesn't include the formation of immune granulomas?

| | | | |
|--------------|----------|---------|---------|
| A- Parasites | B- Metal | C- Talc | D-Fungi |
|--------------|----------|---------|---------|

4- Which of the following are considered Acid Fast Bacilli?

| | | | |
|----------------------------------|------------------------------|--------------------------------|----------------------|
| A- M. Tuberculosis & Actinomyces | B- Schistosoma & Actinomyces | C- M. Tuberculosis & M. Leprae | D- None of the above |
|----------------------------------|------------------------------|--------------------------------|----------------------|

5- Which of the following has a characteristic of having a non-caseating granuloma?

| | | | |
|--------------------|------------------------|------------------|----------------|
| A- Schistosomiasis | B- Cat-scratch disease | C- Actinomycosis | D- Sarcoidosis |
|--------------------|------------------------|------------------|----------------|

6- Which of the following cause a bacterial infection commonly affecting the face and the neck and is caused by a gram positive bacteria ?

| | | | |
|------------|------------------|------------------------|-----------------|
| A- Leprosy | B- Actinomycosis | C- Cat-scratch disease | D- Tuberculosis |
|------------|------------------|------------------------|-----------------|

SAQs

1. Define the main classifications of granulomas according to their pathogenesis.

Slide 10 (3 types)

2. What is the most important cell in granulomatous inflammation?

Epithelioid cells

3. What are the major characteristics of Cat-scratch disease?

Slide 14

| | |
|----------------------|------------------|
| هادي الحمصي ● | البندري العنزي ● |
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